

## Inflammatory bowel disease in the geriatric population

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## 1. ABSTRACT

Inflammatory bowel disease (IBD) is a chronic disease that affects not only the young adults, but also the elderly. The elderly are more vulnerable and at higher risk from complications related to IBD. In this review we focus on IBD important features in the elderly and discuss the disease (1) epidemiology, (2) pathophysiology, (3) clinical manifestations and diagnosis, (4) prognosis, (6) therapy and (7) potential future research directions.

## 2. INTRODUCTION

It is estimated that people aged 65 years and over currently comprise 7.6% of the world population. The World Health Organization (WHO) estimates that, globally, the geriatric population will be 1.2 billion by 2025, and two billion by 2050 (1).

In the United States (US), there has been a dramatic increase in the elderly, especially among women, and this trend is likely to continue for many years to come. For example, during the past 100 years the US population under age 65 years has tripled, while the age group 65 years and older has increased by a factor of more than 12, growing from 3.1 million in 1900 to 38.9 million in 2008. This represents 12.8% of the US population, or over one in every eight Americans. Furthermore, this group is expected to more than double by the middle of the next century, to 82 million people, with most of this growth occurring between 2010 and 2030 (2).

There are many diseases that affect both the elderly and the young patients, however; the way that such disorders and conditions present their prognosis and therapy may need to be modified in patients of advanced

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age based on other comorbidities, current quality of life, and expected lifespan.

Inflammatory bowel disease (IBD) is a chronic disorder that can affect all ages and is generally much more prevalent in younger patients up to age 50. It is often assumed to be confined to this younger group. However, IBD is often seen in elderly individuals aged 65 and older (3). Crohn's disease (CD) and ulcerative colitis (UC) represent the two main forms of IBD. Both UC and CD differ in their pathophysiologic effects on the GI tract and other extra-intestinal organs are involved.

Several studies have suggested that the severity and prognosis of IBD in the elderly is worse, with a higher incidence of life-threatening complications (4; 5; 6; 7; 8; 9). For example, in a nationwide study, older patients with IBD-related hospitalizations have substantial morbidity and higher mortality than younger patients (10). However, more recent studies have reported a more favorable course in the elderly and geriatric population, including a lower risk of surgical and clinical relapse. Therefore, this suggests that the course of IBD may become milder with increasing age and intriguingly, the characteristics of IBD in elderly appear to be different from those in the younger population. Some studies have proposed that the initial age at diagnosis should be part of the disease classification and clinical risk factor stratification (11; 12; 13; 14). Other factors that may explain the improvement in prognosis of IBD for the aged population include early diagnosis, improved treatment, better management of comorbid conditions and advances in medical technology, or even a change in the behavior and pattern of the disease in this unique population.

Critical reviews that focus on IBD on the elderly and geriatric population are relatively few. Therefore, this comprehensive critical review focuses on several important aspects and differences of IBD in the aging geriatric population.

### 3. EPIDEMIOLOGY

The incidence of IBD varies greatly in different geographic locations, and whether this represents regional differences in susceptibility or varying diagnostic capabilities is unclear. Overall, the incidence of IBD has been rising not only in the Western countries, but also in Asia, China, Japan, and Korea (15). According to a series of population-based surveys from Olmsted County, Minnesota, conducted between 1940 and 2000, the incidence rates of CD and UC increased after 1940. Since that time IBD rates have remained stable over the past 30 years up to 1991. Since 1991, the prevalence of UC has decreased by 7%, and the prevalence of CD has increased about 31%. Extrapolating these figures to United States Census data, it is estimated that approximately 1.1 million people had IBD in the United States for the year 2000 (16).

The true incidence in the elderly is hard to determine due to differences in the populations studied and the large number of other bowel disorders in the elderly that may mimic some features of IBD and complicate its

course. In a review of the Medical College of Wisconsin's IBD Center database, approximately 11.8% of 382 UC patients were over the age of 65, while 9% of 916 Crohn's disease patients were in the geriatric age group. Among the elderly UC patients, 16 of 45 (36%) were diagnosed at age 65 or older, while 29 of 83 (34.9%) elderly CD patients presented at age 65 or older (17).

The steady aging of the population can be expected to translate into a growing number of IBD cases diagnosed over the next decade. For example, UC exhibits bimodality in age-specific incidence rates with the second peak occurring at 60 to 70 years of age (18; 19; 20; 21; 22). However, the existence of a second CD incidence peak between 60 and 80 years of age remains controversial.

Ten percent of patients diagnosed with IBD are older than 60 years of age with an equal distribution between CD and UC (23; 24). Many centers have described increasing incidence rates of CD (25) and UC (26) over the past 5 decades. More recently, however, the incidence of CD (23) and UC (24) appears to be stabilizing. Despite this, CD and UC continue to grow more prevalent as a result of the early age of onset and decreased mortality. In one study, older age at CD diagnosis was associated with a greater prevalence of colonic disease and the inflammatory subtype (27).

Large scale epidemiological studies to delineate factors such as cigarette smoking and genetic heterogeneity associated with IBD in the aging and geriatric population is needed.

### 4. PATHOPHYSIOLOGY

The exact etiology of IBD is not known. IBD is a multifactorial disease and there may be a combination of genetic predisposition, environmental influences and immunological abnormalities to trigger the development of IBD in genetically-predisposed individuals. With aging, fundamental alterations in the immune response occur because of general age-related systemic dysregulation of cellular immunity, a phenomenon known as immunosenescence. Immunosenescence is characterized by three main aspects: (1) the shrinkage of the T cell repertoire and the accumulation of oligoclonal expansions (megaclones) of memory/effector cells directed toward ubiquitous infectious agents; (2) the involution of the thymus and the exhaustion of naïve T cells; and (3) a chronic inflammatory status called inflamm-aging (28). The age-associated imbalance between adaptive and innate immunity leads to the pro-inflammatory phenotype with activated innate immunity responses (29) termed this age-related immune status "inflamm-aging" (30). Antigenic stress, either external or inherent, with oxidative stress increases the demands on the innate immunity system and leads to the aging-type of a low-level but chronic inflammatory phenotype (31).

Immunosenescence results in impaired response to antigen exposure with subsequent chronic and inflammatory diseases such as IBD. It would be interesting

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to investigate cellular immunity of IBD in the geriatric population. Common genetic variants (polymorphism) that reside within the genes encoding inflammatory cytokines are candidates to positively or negatively affect immunosenescence. Therefore, depressed T cell responses and T-cell-macrophage interactions in aged and geriatric population is clinically reflected as delayed-type hypersensitivity responses.

### 4.1. Crohn's disease

Crohn's disease can occur anywhere along the gastrointestinal tract and is characterized by transmural inflammation. Lymphoid aggregates can be seen spread across all layers of the bowel wall, but occur primarily in mucosa and submucosa, which is practically diagnostic for Crohn's disease. The pathophysiology of CD is thought to be Th1-mediated. Th1-mediated inflammatory cytokines include IL-12 and IFN-g (32). There are age-associated immune dysfunctions as a consequence of declines in both the generation of new naive T- and B-lymphocytes and in the functional competence of memory populations. Therefore, although not studied, it is expected that Th-1 pathway is altered in CD elderly and geriatric patients and as such contributes to the disease pathophysiology.

### 4.2. Ulcerative colitis

In ulcerative colitis, the inflammation is limited to the mucosa and submucosa. However in active disease, neutrophils can be found infiltrating the crypts with erosions or ulcerations that can penetrate into the submucosa in severe disease. The inflammation is thought to be regulated by Th2-cells, which mediate B cells and antibody responses; however this has not been proven (33).

In a mouse model of colitis, it has been shown that colitogenic CD4 cells may be exhausted over time, become non-functional, and convert to regulatory cells (34). Thus, it is expected that the immunopathogenesis of UC in elderly patients is related to immunosenescence. No data is available in the literature that investigated the immunopathological role of immunosenescence in aged and geriatric patients with IBD. Collectively, basic research is needed to better understand and define the relationship between immunosenescence and IBD in aged and geriatric population.

## 5. CLINICAL MANIFESTATIONS AND DIAGNOSIS

### 5.1. Challenges

The diagnostic work-up of IBD in geriatric patients can be both challenging and time consuming. Several factors make it difficult to determine the etiology of abdominal pain in the older patients. Medical history may be difficult to gather due to depressed mental status or impaired cognition. Even physical exam may not be as reliable, as elderly patients can present with minimal peritoneal signs. Blood tests may not show the usual leukocytosis expected in an inflammatory disease flare.

IBD typically presents with symptoms of abdominal pain, fecal urgency and bloody diarrhea. These

symptoms are not specific to IBD. Several other GI conditions common in older patients such as colitis (due to infection), drugs, malignancy, ischemia, or other inflammatory conditions (such as diverticulitis) can present in a similar manner and even can mimic IBD on radiologic, endoscopic, and histologic testing. In a study by Wagtmans *et al.*, incorrect preliminary diagnosis of CD occurred in 50% of the elderly as opposed to 39% in the young adults, causing delay in the diagnosis of older patients. In this context, diverticulitis and malignancy as incorrect initial diagnosis were frequent (35).

IBD including both UC and CD in the elderly have some differences in presentation and clinical course. (Table 1) In older patients, UC tends to present with left-sided disease or proctitis and a more limited extent of disease, often confined to the rectum. (36) Although the initial attack tends to be more severe, there is a lower incidence of pancolitis. Geriatric patients with CD generally tend to have less abdominal pain and cramping than younger patients, which may be altered sensory perception with aging. Furthermore, CD in elderly patients often manifests with a higher frequency of diarrhea and less bleeding as compared to younger patients. CD in the elderly is often limited to the colon, and ileal disease and stricturing are less frequent. Older patients are less likely to have family history of IBD. Finally, geriatric patients with CD have a higher perforation rate and a higher mortality (37; 38).

### 5.2. Changes in bowel habits

The leading symptom of IBD is diarrhea. In most adult patients, diarrhea is the prevailing symptom that prompts patients to seek medical attention. Eighty five percent (85%) of patients with CD and 70% of patients with UC report at least five bowel movements during the acute phase. The main reason for diarrhea is colonic inflammation, but bile acid and food malabsorption secondary to inflammation in the terminal ileum or proximal small bowel can also cause diarrhea in patients with IBD. In CD many reports have suggested a higher proportion of isolated colonic involvement with a propensity for the rectum and sigmoid in those older than 55 to 60 years of age (39; 40; 41) While typical symptoms of UC like diarrhea, fever, and weight loss are more common in the younger patients, atypical presentations including constipation with little or no diarrhea may be the case in the older patients. Proctocolitis as the first presentation is more common in older patients, and this may be more severe and of longer duration than in younger patients (42; 43).

Elderly patients with UC are more likely to respond to medical therapy and to stay in remission than younger patients (36). However, geriatric patients can have an increased frequency of toxic megacolon with a related high mortality rate (44).

### 5.3. Extraintestinal manifestations

In general, approximately 50 to 60% of patients with IBD suffer from extraintestinal manifestations and approximately 25% have more than one extraintestinal

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**Table 1.** Major Differences in Crohn's Disease and Ulcerative Colitis in the Elderly

Differences	Crohn's Disease	Ulcerative Colitis
Major sites	Ileum	Rectum
Distribution	GI tract; from mouth to anus	Can be more confined to the terminal ileum and rectum
Small bowel affected	Yes	No
Rectal bleeding	Less common	Frequent but less than younger patients
Perianal abscesses and fistulae	Frequent	uncommon
Inflammation	Transmural	Mucosal
Pseudopolyps	No	Yes
Granulomas	Yes	No
Malignant risk	Low	Moderate
Colonic carcinoma risk	Raised	High
Surgery required	In case of complications	Frequent
Pathology	Transmural granulomatous inflammation	Superficial inflammation
Abdominal pain	Frequent	Less frequent
Diarrhea	Less frequent	Frequent but can be masked by other causes for constipation
Oral and facial manifestations	Frequent	Rare
Folate and Iron deficiencies	Frequent	Frequent
Others deficiencies	B12	Uncommon
Major clinical complications	Weight loss, GI obstruction, perianal fissures, fistulas, abscesses, arthralgia, sclerosing cholangitis, renal complications	Colorectal carcinoma, life threatening toxic megacolon, colon perforation, arthralgia, conjunctivitis, uveitis, iritis, sacro-iliitis, finger clubbing, erythema nodosum, pyoderma gangrenosum, sclerosing cholangitis, gallstones, renal calculi, arthritis, hemorrhage, stricture

manifestation. It is not clear whether there is any difference in the likelihood of developing extraintestinal manifestations in the elderly with IBD. In one study by Heresbach and colleagues, extra-intestinal symptoms were seen in 3% of patients (45). Other reports did not find any major differences in the incidence of extraintestinal manifestations between older and younger patients with CD (35, 40, 46). Those manifestations can vary from arthropathies with mono- or polyarthritis accounting for the most frequent extraintestinal manifestation. Other manifestations can include cutaneous lesions like erythema nodosum (EN), pyoderma gangrenosum (PG), ulcer lesions of the gingival or cheek mucosa. Ophthalmologic manifestations, including uveitis and iritis, are uncommon in IBD and occur in less than 10% of cases, with predominance in CD. Biliary and liver manifestations like fatty liver degeneration are commonly seen, and can be followed by primary sclerosing cholangitis (PSC), cholelithiasis, and granulomatous hepatitis. Approximately 20% to 30% of patients with CD suffer from osteopenia and about 7% of the patients develop signs of clinically relevant osteoporosis (47). Although osteoporosis is a common side effect of chronic glucocorticoid therapy, it appears that inflammatory activity of IBD itself is a risk factor; duration as well as the course of disease is associated with an increasing risk of developing osteoporosis. Patients with IBD are at greater risk of developing metabolic bone disease, both osteoporosis and osteomalacia. This may result from a decreased absorption of vitamin D and frequent use of steroids. Appropriate monitoring and treatment for osteoporosis is warranted. Nephrolithiasis is seen in up to 10% of patients with ileal manifestation of CD or after ileal resection.

### 5.4. Orofacial manifestations

A wide range of oral lesions has been clinically reported in IBD patients especially with CD; however, many of the abnormalities described are relatively non-specific and can be confused with other lesions in the

elderly. Pyostomatitis vegetans, presents as multiple, friable pustules, erosions, and ulcerations of oral mucosa in UC patients and can reflect the presence of active intestinal disease and often manifests before diagnosis of UC (48). Aphthous ulcers are also common in patients with IBD and have been reported to with an incidence of 4.1% in CD and 1.5% in UC (49). Other manifestations in IBD include cobblestone-like raised lesions, mucosal tags, hyperplastic folds, redness, ulcers, yellowish pustules, irregular folds and swelling of the oral gingival, facial swelling and angular cheilitis. (50; 51; 52).

The most common affected sites and manifestation of CD are on the buccal mucosa, lips, and cheeks. While the less common sites are gingival, alveolar mucosa and the palate which are usually presented with granular, erythematous swelling and ulcerations (53; 54). Unlike CD, the oral features of UC are rare, but may include anemia related lesions, hemorrhagic ulcers, chronic ulceration (pyostomatitis gangrenosum) and pyostomatitis vegetans.

The oral manifestation of the disease in geriatric patients may be confused with other diseases and have a wide range differential diagnosis. Nutritional deficiencies, malabsorption, local trauma such as denture-related irritation, lichen planus, shingles or varicella zoster virus, candida, salivary gland hypofunction, leukoplakia, Lichenoid mucosal lesions related to a variety of medications commonly prescribed in older patients (eg, acyclovir, gold salts, methyl dopa, thiazide diuretics) and anemia relate to folic acid, B12 or Iron are not uncommon in elderly patients and can present with similar lesions to oral lesion found in IBD with symptoms such as burning mouth, glossitis or angular stomatitis, ulcerations, xerostomia and other mucosal changes (55; 56).

## 6. PROGNOSIS AND QUALITY OF LIFE

While IBD in the elderly can limit quality of life due to its symptoms and medical treatment related side

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**Table 2.** IBD Treatment complications in the elderly

Treatment method	Possible complications to consider
Aminosalicylates	Nephrotoxicity like chronic interstitial nephritis
Corticosteroids	Aggravate or precipitate diabetes, hypertension, congestive heart failure and cataracts
	Compression fractures
	GI perforation
Thiopurine	Pancreatitis
Antimetabolites	Leukopenia
Infliximab	Increase risk for infections and malignancies

effects. The prognosis in the elderly is usually good; however, there is an increased mortality compared with younger patients, which is probably due to the presence of coexistent diseases and higher co morbidities. In the early 1960s, the course of IBD in the elderly was felt to be worse than that for younger patients. However, more recent and emerging data suggest the differences between the two groups may only be marginal. A review of 244 patients who are over 60 years old and have IBD found that response to therapy and need for surgery and development of complications was no different than in younger patients under 60 years (57). The mortality rate was higher, 2.4% compared to 0.8%, although the duration of this study was not stated. The pattern of CD was different with colonic disease being relatively more common in the elderly, 52% compared to 28.2%.

Overall extensive involvement is a poor prognostic factor; conversely, isolated small bowel CD and UC carry particularly good prognoses. Another study of CD in the elderly suggested a good prognosis in colonic disease but a worse in ileal or ileocolonic disease (58). A study of elderly patients with UC revealed no difference in prognosis compared with younger patients, but they were more likely to be admitted to a hospital or to receive systemic steroids (59).

Reported postoperative recurrence rates vary widely, in part owing to differences in the criteria used for recurrence. Recurrence rate in older patients with CD is consistently reported to be lower than younger patients with 43% developing recurrence compared with the young adults 64% according to Wagtmans *et al* (35).

## 7. TREATMENT

The general approach for IBD therapeutic interventions in elderly and younger patients is very similar. However, special considerations in the geriatric population include any comorbidities, potential drug interactions, and side effects of medications. (Table 2) Additionally, medication compliance may be an issue in the presence of cognitive or functional impairment. Traditionally, the goals of therapy have been to eliminate all symptoms related to IBD. More recently, other goals have been advocated such as improving a patient's quality of life and reducing hospitalization, surgery, and improving mucosal healing. The standard therapies available to a clinician include 5-aminosalicylates, sulfasalazine, antimicrobial therapy, corticosteroids, immunosuppressive agents, and monoclonal antibodies (MAbs). The only commercially available MAbs include the anti-tumor

necrosis factor (TNF) antibodies (eg, infliximab, adalimumab, and certolizumab pegol), and natalizumab, a MAb directed against the alpha 4-integrin (60; 61; 62; 63; 64). Adalimumab, certolizumab pegol, and natalizumab are not currently indicated for UC but rather for CD. Antimicrobial agents lack efficacy in UC and their use is not advocated (65; 66).

Therapy is sequential, with the first priority to treat acute disease, followed by the maintenance of remission. The general principles of treating IBD are the same regardless of the patient's age. Mild flares of IBD are managed best by aminosalicylates delivered topically (e.g., by enema in left-sided UC) or orally.

### 7.1. Aminosalicylates

Aminosalicylates are the drugs of choice for maintaining remission; however, side effects can include nephrotoxicity such as chronic interstitial nephritis especially in the elderly. Renal function must be monitored, especially in the first year of treatment. Topical use as suppositories and enemas alone or in combination with oral form are effective among UC patients with proctitis and can be beneficial minimizing the systemic side effects. Fecal incontinence due to compromised anal sphincter is common in the elderly and can be a limiting factor.

Aminosalicylates can reduce the bioavailability of digoxin, possibly requiring higher dosages. Aminosalicylates can also increase levels of active metabolites of 6-MP and azathioprine, requiring careful attention with concurrent use. Awareness is needed in patients on allopurinol as it increases active metabolites of 6-MP and azathioprine.

### 7.2. Corticosteroids therapy

More severe flares of IBD (such as unresponsive to aminosalicylates) typically are managed with oral glucocorticoids. Induction therapy with corticosteroids is a highly effective strategy. Population-based studies have demonstrated that after 30 days prednisone results in remission in 48% to 58% of patients, response in 26% to 32%, and lack of response in 16% to 20% (67; 68).

Although glucocorticoid therapy has a host of short-term and long-term side effects in all age groups, the elderly are particularly prone to the complications of glucocorticoid therapy. Systemic steroids should be tapered rapidly as tolerable, and preferably within 8-10 weeks. Long-term glucocorticoids in IBD generally are not recommended for the maintenance of remission due to increase risk of complications. For example, glucocorticoids may aggravate or precipitate diabetes, hypertension, congestive heart failure, osteoporosis, glaucoma, and cataracts. Among other side effects in the elderly are insomnia, euphoria, mania, and, depression upon withdrawal (particularly in those suffering from bipolar and history of psychiatric disorders). In a study by Thomas and colleges, the most commonly reported side effects were compression fractures (16% of subjects) and hypertension (12% of subjects) (69). Patients with UC on steroid treatment are more prone to GI perforation.

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Enteric release budesonide is also an essential option to the treatment regimen in the elderly patients. It can be used as a first-line medication for the induction remission of mild to moderate CD involving the terminal ileum or ascending colon. Budesonide works topically and has a high first-pass metabolism in the liver, minimizing but not eliminating steroid-related side effects (70).

Among list of drug interaction is cyclosporine which resulted in increased risk of seizures when used along with methylprednisolone. Use of cyclosporine also necessitates avoidance of potassium-sparing diuretics, live vaccines, and nephrotoxic drugs.

### 7.3. Thiopurine Antimetabolites

Studies to evaluate the safety of 6-mercaptopurine (6-MP) and azathioprine have not been performed specifically in the aged population. Retrospective case series designed to assess the toxicity of these agents have included elderly subjects. According to studies by Present and O'Briain no particular problems were reported with the use of 6-MP in older patients (71, 72). Generally, it has been estimated that immunosuppressive therapy with azathioprine or 6-MP has to be discontinued in roughly 10% of patients because of side effects (72). Pancreatitis is one of the commonest side effects and occurs in about 3% of patients and severe bone marrow depression and leukopenia occurs in approximately 2% of patients. Regardless of age, immunosuppressive agents such as azathioprine (AZA), 6-MP and methotrexate (MTX) have been studied for induction of active moderate-to-severe corticosteroid-dependent IBD (73; 74). In a meta-analysis examining the use of AZA/6-MP, the odds ratio for response for active CD was 3.09; 16 weeks of parenteral MTX at a dose of 25 mg weekly led to remission in 39% of patients. However, neither agent is rapidly acting for the acute flare. They generally require concomitant corticosteroids for induction therapy. It is recommended to monitor complete blood count and liver function tests when using 6-MP or azathioprine.

### 7.4. Infliximab

Although there is insufficient data to assess the safety of infliximab in patients aged 65 and older with IBD, this agent has been used safely for other indications in the elderly including rheumatoid arthritis (RA) and ankylosing spondylitis (AS) treatment. The ageing process induces a decline in the function and control of the immune system. Thus, the prevalence of adverse effects of anti-TNF- $\alpha$  agents, and particularly of infections, might be increased in the elderly population and may require caution.

In the ATTRACT (Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy) trial, 72 patients older than age 65 were treated with infliximab, and there was no difference in the observed effectiveness or safety of infliximab between older and younger patients (75). However, in another study by Ljung (76) assessing the potential toxicity of Infliximab in IBD concluded that Infliximab was efficacious as an anti-inflammatory

treatment when assessed on patients with IBD (76). However, there appears to be a significant risk of deleterious and fatal adverse events, particularly in elderly patients with severe attacks of IBD, and off label use of infliximab in IBD should be avoided until efficacy is proven in randomized controlled trials.

Generally patients treated with infliximab are at increased risk for infections, some progressing to serious infections leading to hospitalization or death. These infections have included bacterial sepsis, tuberculosis, invasive fungal and other opportunistic infections. Evaluation of potential latent tuberculosis and treatment if necessary prior to initiation of therapy is recommended. Lymphoma and other malignancies have also been reported. Exacerbation of heart failure, bone marrow suppression and hepatitis among other side effect and complications of infliximab treatment. Rare post marketing cases of hepatosplenic T-cell lymphoma, usually fatal, have been reported in patients with CD and UC treated with infliximab. All of these hepatosplenic T-cell lymphomas with infliximab have occurred in patients on concomitant treatment with azathioprine or 6-mercaptopurine.

### 7.5. Cyclosporine

In younger patients with sever UC Cyclosporine has a first place as salvage therapy because of its short half-life and its established short-term efficacy in patients who fail steroids treatment. However the drug should be avoided in frail elderly patients with significant comorbidity. Cyclosporine can lead to side effects as worsening hypertension, renal failure, hypertrichosis and neurotoxicity. An accurate quantification of creatinine clearance is essential in the elderly prior to treatment consideration.

## 8. POTENTIAL FUTURE RESEARCH DIRECTIONS

Although chronic IBD have been described in the modern medical literature for more than 100 years, their etiology and pathogenesis are still not completely understood. A large body of evidence support interrelated genetic and environmental factors that contribute to mucosal immune function dysregulation (77; 78; 79). Therefore, basic science researchers have evaluated different novel small molecule and biologic agents that target inflammation signaling pathways. For example, anti-tumor necrosis factor agents such as adalimumab, certolizumab pegol, and golimumab, as well as anti-IL12 drugs, basilixumab and visilizumab. Emerging research also has identified multiple genes that may play a part in IBD like the NOD-2 gene with possible link to IL-10 that may drive the persistent of inflammation. Other possible link is also between bacterial pathogens such as *E. coli* and IBD.

A new target called N6022, an inhibitor of s-nitrosoglutathione reductase (GSNOR), is currently in phase I testing. N6022 has the potential to be an important new treatment for acute exacerbations of IBD. GSNOR breaks down s-nitrosoglutathione (GSNO), reducing the body's pool of GSNO. In the gut, GSNO supports barrier function and maintains the integrity of the gut surface.

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The discovery CD4<sup>+</sup> effector T helper (Th) cells that selectively produce IL-17 also has provided exciting new insights into immune regulation, host defense, and the pathogenesis of autoimmune and other chronic inflammatory disorders like IBD. AZ 17 agent is a bispecific molecule composed of two single-chain variable fragments (scFvs) linked using a specialized platform technology. It inhibits two upstream cytokines involved in the Th17 pathway and currently been studied as a potential treatment for CD.

The future IBD research undoubtedly will deliver more innovative methods in the diagnosis and management of this chronic and often devastating illness especially in the geriatric population which is prone to more long term complications. Thus, novel targeted therapies with minimal side effects and complications are needed in such patient population. Despite advances in technology and diagnostics tools available further research trials is needed to achieve a clear standard guidelines on how to provide a quality care and safe treatment for IBD in the elderly.

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